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Citric acid – Method for the determination of citric acid in workplace air using high performance liquid chromatography (HPLC)

Air Monitoring Method – Translation of the German version from 2019

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Keywords

citric acid, hazardous substances, air analysis, analytical method, workplace measurement, high performance liquid chromatography

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Abstract

This analytical method is a validated measurement procedure for the determination of citric acid [77-92-9] in workplace air in a concentration range of one tenth up to twice the currently valid OEL or MAK value of 2 mg/m³ I. Sampling is performed by drawing a defined volume of air through a glass fibre filter, which is inserted in a GSP sampling system using a suitable flow-regulated pump with a volumetric flow rate of 10 l/min or 3.5 l/min. For sampling 2 hours or 15 min (checking the short-term value) can be used. The collected citric acid is extracted with diluted caustic soda and analysed by means of high performance liquid chromatography using an UV detector. The quantitative determination is based on a calibration function obtained by means of a multiple-point calibration. The absolute limit of quantification (LOQ) is 12 ng and the relative LOQ is 0.005 mg/m³ based on an air sample volume of approx. 1200 l (0.014 mg/m³ based on air sample volume of 420 l) or 0.04 mg/m³ based on an air sample volume of approx. 150 l (for short-term value) (0.11 mg/m³ based on air sample volume of 52.5 l). The mean recovery was 100% and the expanded uncertainty for the overall measurement method was 18%.

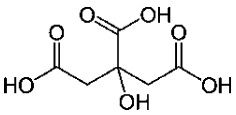
Method number	1
Application	Air analysis
Analytical principle	High performance liquid chromatography (HPLC)

1 Characteristics of the method

Repeatability:	Standard deviation (rel.): s = 0.5% at concentrations of 72 and 530 µg/ml	
Reproducibility:	Standard deviation (rel.): s = 0.9% at a concentration of 500 µg/ml	
Expanded uncertainty:	U = 18% in the concentration range from 0.2 to 4 mg/m³ and for an air sample volume of 1200 litres.	
	U = 18% in the concentration range from 2 to 8 mg/m³ and for an air sample volume of 150 litres.	
Recovery:	η = 1 (100%) at an air sample volume of 1200 l.	
Limit of quantification:	Absolute:	12 ng
	Relative:	0.005 mg/m³ for an air sample volume of 1200 l
		0.014 mg/m³ for an air sample volume of 420 l
		0.04 mg/m³ for an air sample volume of 150 l
		0.11 mg/m³ for an air sample volume of 52.5 l
Sampling recommendations:	Sampling time:	120 min
	Air sample volume:	1200 l or 420 l
	For short-term exposure limit measurements:	15 min; 150 l or 52.5 l

2 Description of the substances

Citric acid [77-92-9]



Synonyms: 2-hydroxypropane-1,2,3-tricarboxylic acid; 3-carboxy-3-hydroxypentane-1,5-dioic acid; E330

Citric acid is a colourless and odourless solid (molar mass 192.43 g/mol, melting point 153 °C, boiling point decomposition: from 175 °C, vapour pressure 7.3×10^{-9} hPa at 25 °C). It is a carboxylic acid, which is soluble in water (600 g/l) and it belongs to the fruit acids.

Citric acid is one of the most common acids in the plant kingdom. It occurs naturally particularly in citrus fruit, such as lemons, limes, oranges, mandarins and grapefruit; the juice of a lemon contains e.g. approx. 5 to 7% of citric acid. Furthermore, it occurs in e.g. apples, pears, raspberries, red currants and black currants, kiwis and mushrooms. Citric acid in form of its salts (citrates) is an important intermediary metabolic product of energy metabolism (citric acid cycle) and is thus a component of each living cell in an organism.

Besides extraction from citrus fruit, citric acid is also biotechnologically produced with the help of micro-organisms. Aspergillus niger mould is used for this purpose in particular, whereby maize and molasses serve as a growing medium.

Citric acid (E 330) and its salts are important additives in the food industry, where they are used as preservatives, as they are effective in inhibiting oxidation processes that accelerate the decomposition of food. Furthermore, it is used as a complexing agent and acidifier. As an acidity regulator citric acid maintains the desired pH value of food constant. Additionally, citric acid is used as a cleansing agent, in particular for descaling.

The MAK value of citric acid is 2 mg/m³ I. The peak limit has been assigned an excursion factor of 2 in Category I (DFG 2018). Detailed information on the toxicity of citric acid can be found in the toxicological-occupational health documentation of MAK values (Greim 1998; Hartwig and MAK Commission 2018).

3 General principles

The analytical method described here can be used to determine citric acid in workplace air in a concentration range of one tenth up to twice the currently valid MAK value of 2 mg/m³ I and for checking the peak limit, which has been assigned an excursion factor of 2 (DFG 2018).

Sampling consists of a flow-regulated pump drawing a defined volume of air through a glass fibre filter located in a GSP sampling system. The sampling head used is fitted with an intake cone suitable for a flow rate of 10 l/min, which is equivalent to a suction rate of approx. 1.25 m/s and thus meets the requirements of DIN EN 481 (DIN 1993) for inhalable particles. Alternatively, an intake cone suitable for a flow rate of 3.5 l/min can also be used. Citric acid deposited on the filter is extracted with dilute sodium hydroxide and analysed by means of high-performance liquid chromatography using an UV detector. The quantitative determination is carried out on the basis of two multiple-point calibrations.

4 Equipment, chemicals and solutions

4.1 Equipment

- Glass fibre filter, e.g. MN 85/90 type, free from binding agents, Ø 37 mm
- Personal sampling system) with a sampling head for the inhalable fraction (GSP) and an intake cone for 10 l/min (Figure 1) or an intake cone for 3.5 l/min, supplied by DEHA Haan & Wittmer GmbH, 71296 Heimsheim, Germany
- Filter cassettes for the GSP sampling system, supplied by DEHA Haan & Wittmer
- Pump for personal air sampling, flow rate 10 l/min and 3.5 l/min, e.g. SG10-2, from GSA Gesellschaft für Schadstoffanalytik, 40880 Ratingen, Germany
- Rotameter, e.g. Influx 1–13 litres, from DEHA Haan & Wittmer
- High performance liquid chromatograph with UV detector or DAD, e.g. Agilent 1200, 76337 Waldbronn, Germany
- Separation column, e.g. IC-PAK Ion Exclusion (7.8 × 150) mm, 7 µm, from Waters, 65760 Eschborn, Germany
- Analytical balance
- Ultrasonic bath
- Benchtop centrifuge, 10 000 rpm, e.g. Universal 320R, from Hettich GmbH, 78532 Tuttlingen, Germany
- Volumetric flasks, 10 ml and 100 ml
- Centrifuge vials, 10 ml

- Disposable syringes
- Automatic positive displacement pipette, e.g. Multipette pro (1 µl to 10 ml) from Eppendorf, 22366 Hamburg, Germany
- Autosampler vials, nominal volume 2 ml
- Disposable filters, pore size 0.45 µm, regenerated cellulose, Ø 30 mm

Fig. 1 GSP sampling head (DGUV 2016)

4.2 Chemicals

- Water for chromatography, e.g. from Merck, Darmstadt, Germany, Order No. 1.15333
- 0.1 mol/l sodium hydroxide solution, e.g. from Merck, Order No. 1.09141
- o-Phosphoric acid (85%) p.a., e.g. from Merck, Order No. 1.00573
- Citric acid e.g. from Sigma-Aldrich, Order No. C0759

4.3 Solutions

Eluent: 0.00333 mol/l phosphoric acid

222 µl of 85% phosphoric acid (15 mol/l) are added into a 1000 ml volumetric flask, into which approximately 500 ml of water (for chromatography) have been previously placed. The volumetric flask is then filled to the mark with water (for chromatography) and shaken.

Stock solution 1: Citric acid (9.59 mg/ml)

968.18 mg of citric acid (99.1%) are weighed exactly into a 100 ml volumetric flask. The volumetric flask is then filled to the mark with water (for chromatography) and shaken. The concentration of citric acid is 9.595 mg/ml.

Calibration standards for obtaining two calibration functions for the lower and upper concentration ranges.

Six calibration solutions (to determine the lower concentration range) are prepared from stock solution 1 as follows:

The volumes of stock solution 1 listed in Table 1 are dosed into 10 ml volumetric flasks, into which approx. 5 ml of sodium hydroxide solution have been previously placed. The volumetric flasks are then filled to the mark with sodium hydroxide solution and shaken.

Tab. 1 Pipetting scheme for the preparation of six calibration standards of citric acid in the lower concentration range

Calibration standard	Stock solution 1: [µl/10 ml]	Concentration [µg/ml]
Calibration standard I (blank sample)	0	0
Calibration standard II	25	23.99
Calibration standard III	50	47.97
Calibration standard IV	75	71.96
Calibration standard V	100	95.95
Calibration standard VI	125	119.9

Eight calibration solutions to determine the upper concentration range are prepared from stock solution 1 as follows:

The volumes of stock solution 1 listed in Table 2 are dosed into 10 ml volumetric flasks, into which 5 ml of sodium hydroxide solution have been previously placed. The volumetric flasks are then filled to the mark with sodium hydroxide solution and shaken.

Tab. 2 Pipetting scheme for the preparation of the calibration standards of citric acid in the upper concentration range

Calibration standard	Stock solution 1: [µl/10 ml]	Concentration [µg/ml]
Calibration standard I (blank sample)	0	0
Calibration standard II	100	95.95
Calibration standard III	250	239.9
Calibration standard IV	400	383.8
Calibration standard V	550	527.7
Calibration standard VI	700	671.6
Calibration standard VII	850	815.6
Calibration standard VIII	1000	959.5

Two control standards are prepared.

Stock solution for the control standard: Citric acid (9.91 mg/ml)

100 mg of citric acid (99.1%) are weighed exactly into a 10 ml volumetric flask. The volumetric flask is then filled to the mark with water (for chromatography) and shaken. The concentration of citric acid is 9.91 mg/ml.

Control Standard 1: Citric acid (approx. 74.3 µg/ml)

A pipette is used to add 75 µl of the control stock solution to a 10 ml volumetric flask into which several ml of sodium hydroxide solution have already been placed. The volumetric flask is then filled to the mark with sodium hydroxide solution and shaken. The concentration of citric acid is approx. 74.3 µg/ml.

Control Standard 2: Citric acid (approx. 545.1 µg/ml)

A pipette is used to add 550 µl of the control stock solution to a 10 ml volumetric flask into which several ml of sodium hydroxide solution have already been placed. The volumetric flask is then filled to the mark with sodium hydroxide solution and shaken. The concentration of citric acid is approx. 545.1 µg/ml.

Stock solution 2: Citric acid (1.485 mg/ml)

149.83 mg of citric acid (99.1%) are weighed exactly into a 100 ml volumetric flask. The volumetric flask is then filled to the mark with water (for chromatography) and shaken. The concentration of citric acid is 1.485 mg/ml.

Calibration standards for the determination of the limit of quantification.

Ten calibration solutions are prepared from stock solution 2 as follows:

The volumes of stock solution 2 listed in Table 3 are dosed into ten 10 ml volumetric flasks, into which several millilitres of sodium hydroxide solution have been previously placed. The volumetric flasks are then filled to the mark with sodium hydroxide solution and shaken.

Tab. 3 Pipetting scheme for the preparation of the calibration standards of citric acid for determining the limit of quantification

Calibration standard	Stock solution 1 [µl/10 ml]	Concentration [µg/ml]
Calibration standard I (blank value)	0	0
Calibration standard II	25	3.71
Calibration standard III	50	7.42
Calibration standard IV	75	11.14
Calibration standard V	100	14.85
Calibration standard VI	125	18.56
Calibration standard VII	150	22.27
Calibration standard VIII	175	25.98
Calibration standard IX	200	29.7
Calibration standard X	225	33.41

5 Sampling and sample preparation

5.1 Sampling

A glass fibre filter is inserted into the GSP sampling head and the system is connected to a flow-regulated pump at the beginning of sampling. The GSP sampling system is fitted with an intake cone that ensures a flow rate of 10 l/min. Sampling periods of 15 minutes (monitoring the peak limit) and two hours can be selected. At a sampling period of 15 minutes this is equivalent to an air sample volume of approx. 150 litres and two hours is equivalent to an air sample volume of approx. 1200 litres. Alternatively, an intake cone suitable for a flow rate of 3.5 l/min can also be used. In this case the air sample volumes for sampling periods of two hours and 15 minutes are 420 litres and 52.5 litres. Sampling can be carried out as stationary or personal sampling. After sampling, the flow rate must

be tested for constancy. If the deviation from the adjusted flow rate is greater than ±5%, it is advisable to discard the sample (DIN 2014). The filter cassette with the loaded filter is sealed with the supplied caps.

One blank sample (field blank) must be included in every sample series. This differs from the analytical sample in that no sample air was drawn through the filter. This blank sample is then stored and analysed in the same manner as the other samples.

5.2 Sample preparation

For sample preparation the filter is transferred to a 10 ml centrifuge vial and immersed in 5 ml of sodium hydroxide solution. After vigorous manual shaking, the sample is extracted by treating it in the ultrasonic bath for 25 minutes and then it is centrifuged for 10 minutes at 10 000 rpm. Sample liquid is withdrawn from the supernatant solution of the prepared sample using a disposable syringe, the liquid is filtered through a disposable syringe filter into an autosampler vial and analysed. The blank sample (field blank) must also be prepared in the same manner as the sample solution.

Additionally, several millilitres of sodium hydroxide solution are pipetted into an autosampler vial and analysed in order to determine the reagent blank value (lab blank).

6 Operating conditions for chromatography

The analytical measurements are performed with a combination of instruments comprising a HPLC system with a pump, column oven, degasser and autosampler as well as a UV detector or a DAD.

Apparatus:	High performance liquid chromatograph with UV detector or DAD, e.g. Agilent 1200	
Separation column:	IC-PAK Ion Exclusion: 150 × 7.8 mm, particle size 7 µm, 50 Å	
	Length:	15 cm
	Inner diameter:	7.8 mm
Column temperature:	20 °C	
Eluent:	0.00333 mol/l phosphoric acid (isocratic)	
Flow rate:	0.8 ml/min	
Measured wavelength:	210 nm; bandwidth 4 nm	
Injection volume:	10 µl	

7 Analytical determination

10 µl of the prepared sample solution as described in Section 5.2 are injected into in the HPLC for the analytical determination and analysed under the conditions stated in Section 6. Depending on the concentration of citric acid in a sample, either the calibration function in the lower or upper concentration range is used for evaluation. If the measured concentrations are above the calibration range, then suitable dilutions with sodium hydroxide solution must be prepared and the analysis must be repeated. Furthermore, the prepared blank (field blank) and the reagent blank value (lab blank) must be analysed in the same manner as the analytical samples.

8 Calibration

The calibration standards prepared according to Section 4.3 are analysed as described in Sections 6 and 7 in order to obtain both the calibration functions. The peak areas obtained are plotted versus the corresponding concentrations and one calibration curve each is prepared for the lower and upper range.

The two control standards described in Section 4.3 are used to check the calibration functions every working day.

9 Calculation of the analytical result

The concentration of citric acid is calculated using Equation (1) as follows:

$$\rho = \frac{X \times E \times 100}{V \times Wf} \quad (1)$$

where:

ρ	is the mass concentration of citric acid in the ambient air in mg/m³
X	is the concentration of citric acid in the prepared sample solution after deduction of the content of the field blank in µg/ml
E	is the extraction volume in ml (in this case 5 ml)
V	is the air sample volume in litres
Wf	is the recovery in %

10 Reliability of the method

The characteristics of the method were calculated as stipulated in DIN EN 482 (DIN 2015), DIN EN 13890 (DIN 2010) and DIN 32645 (DIN 2008).

10.1 Precision

The repeatability was determined by analysing one calibration standard each in the medium concentration range of the calibration function on six different days. The relative standard deviations obtained for both concentrations were 0.5%.

10.2 Recovery and reproducibility

In order to determine the recovery six filters were each spiked with 10 mg of citric acid. A reduced amount would have been an advantage for checking the MAK value. 10 mg was chosen as the least amount to be weighed in to minimise weighing errors. Then 1.2 m³ of air was drawn through the filters and the filters were prepared according to Section 5.2. The sample solutions were diluted by 1/4 with sodium hydroxide solution (e.g. 200 µl of sample solution and 600 µl sodium hydroxide solution) before analysis by means of HPLC (see Sections 6 and 7).

Reference values were determined by dosing 5 ml of sodium hydroxide solution each into six centrifuge vials and then adding 10 mg of citric acid. The reference samples were prepared in the same manner as the analysis samples, diluted by 1/4 with sodium hydroxide solution and analysed.

Based on the theoretical citric acid content, the determined reference values and recoveries were between 98 and 102%. Statistically the recoveries were not significantly different from the reference values.

The recovery was 100%. The reproducibilities of the reference values and recoveries were around 0.9%.

10.3 Expanded uncertainty of the entire procedure

The measurement uncertainty is obtained by estimation of all the relevant influencing parameters (bottom-up method) (DIN 2010, 2015). The uncertainty of the entire method and therefore also that of the analytical result consists principally of the following uncertainty contributions:

- the air sample volume U_A,
- the sampling apparatus U_{SA},
- the extraction volume U_E,
- the relative recovery U_R,
- as well as the influences on the measurement values $U\rho$, in particular the scatter of the calibration function, the calibration standards and calibration stock solution as well as the laboratory's own repeatability (precision).

The combined uncertainty of the measurement value is concentration-dependent. It is obtained from the uncertainties of the calibration graphs, the calibration stock solution, the preparation of the calibration solution and the results of the precision.

The combination of all uncertainty contributions results in the concentration-dependent combined uncertainty U_{comb}.

The corresponding expanded uncertainty U_{exp}, which simultaneously represents the substance and concentration-dependent measurement uncertainties of the entire procedure, is obtained by multiplication with a probability factor (e.g. k = 2 for 95% certainty). The determined uncertainty contributions are listed in Table 4, whereby a distinction is made between a **l**ow, **m**edium and **h**igh concentration for a 15-minute sampling period. The corresponding combined and expanded uncertainties for a 15-minute sampling period are listed in Table 5.

Tab. 4 Uncertainties for a 15-minute sampling period of citric acid in %

U_A	U_{SA}	U_E	U_R	$U\rho_{-h}$	$U\rho_{-m}$	$U\rho_{-l}$
3.3	8.5	0.2	1.3	1.8	1.9	1.4

Tab. 5 Combined and expanded uncertainties for a 15-minute sampling period in %

U_{comb-h}	U_{comb-m}	U_{comb-l}	U_{exp-h}	U_{exp-m}	U_{exp-l}
9.0	9.2	9.1	**18**	**18**	**18**

Based on a sampling period of 15 min, the concentrations were 8 mg/m³ or 4 and 2 mg/m³.

As the uncertainty contributions e.g. for the extraction volume and the sampling apparatus used for a sampling period of 120 minutes are no different for a sampling period of 15 minutes, Table 6 only lists the measurement uncertainties that differ. Table 6 includes the combined and expanded measurement uncertainties at three different concentrations.

Tab. 6 Uncertainties for a 120-minute sampling period of citric acid in %

U_A	$U\rho_{-h}$	$U\rho_{-m}$	$U\rho_{-l}$	U_{comb-h}	U_{comb-m}	U_{comb-l}	U_{exp-h}	U_{exp-m}	U_{exp-l}
2.6	0.9	1.8	1.6	9.0	9.2	9.1	**18**	**18**	**18**

Based on a sampling period of 120 min, the concentrations were 4 mg/m³, 1 mg/m³ and 0.2 mg/m³.
where:

U_A is the uncertainty of the air sample volume

U_{SA} is the uncertainty of the sampling apparatus

U_E is the uncertainty of the extraction volume

U_R is the uncertainty of the recovery

$U\rho_{-h}$ is the uncertainty of the measured value at a **h**igh concentration (includes precision and scatter of the calibration function)

$U\rho_{-m}$ is the uncertainty of the measured value at a **m**edium concentration (includes precision and scatter of the calibration function)

$U\rho_{-l}$ is the uncertainty of the measured value at a **l**ow concentration (includes precision and scatter of the calibration function)

$U_{comb-\boldsymbol{h}}$ is the combined uncertainty at a **h**igh concentration

$U_{comb-\boldsymbol{m}}$ is the combined uncertainty at a **m**edium concentration

$U_{comb-\boldsymbol{l}}$ is the combined uncertainty at a **l**ow concentration

U_{exp-h} is the expanded uncertainty at a **h**igh concentration

U_{exp-m} is the expanded uncertainty at a **m**edium concentration

U_{exp-l} is the expanded uncertainty at a **l**ow concentration

10.4 Limit of quantification

The limit of quantification for citric acid was determined from a 10-point calibration in the concentration range of 0 to 33.41 µg/ml (see Table 3) as stipulated in DIN 32645 (DIN 2008) with P = 95% and k = 3.33.

The limit of quantification for citric acid was 1.2 µg/ml. Based on an air sample volume of 1.2 m^3 (1200 l), this is equivalent to a relative limit of quantification of 0.005 mg/m^3 and at an air sample volume of 150 l it is equivalent to a relative limit of quantification of 0.040 mg/m^3 (short-term exposure limit). Based on an air sample volume of 420 litres (2 hours at 3.5 l/min), this is equivalent to a relative limit of quantification of 0.014 mg/m^3, and at an air sample volume of 52.5 litres, it is equivalent to a relative limit of quantification of 0.11 mg/m^3 (short-term exposure limit).

10.5 Storage stability

Storage stability experiments showed that the spiked filters as well as the prepared sample solutions and calibration standards are stable for at least three weeks when stored at room temperature.

10.6 Interference

The analytical procedure by means of high-performance liquid chromatography and UV detection is specific and robust under the conditions stated here. No interference from e.g. other organic acids was detected. Blank values are also taken into account due to the parallel sample work-up of the prepared field blanks; however, no blank values were detectable.

9 Discussion

The analytical method described here is suitable for determination of citric acid in workplace air in a concentration range of 0.005 to 4 mg/m³ at a sampling period of 2 hours and for establishing the short-term value (15 minute) in the concentration range of 0.04 to 32 mg/m³.

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Appendix

Precision and accuracy by means of comparative measurements

The precision and accuracy of the measurement method was checked by comparative measurements. For this purpose, twelve glass fibre filters were each spiked with 12 mg of citric acid. Then six filters were analysed in the laboratory of the developer (BGN – *German Social Accident Insurance Institution for the Foodstuffs Industry and the Catering Trade*) and six filters in the laboratory of the examiner (LGL – *Bavarian State Office for Health and Food Safety*). Analysis in the laboratory of the developer was carried out by means of high-performance liquid chromatography (see Sections 5.2 and 6), while photometry after enzymatic reaction (R-Biopharm 2012) was used to check the method. The results of the recoveries of the comparative measurements are shown in Table 7.

Tab. 7 Results of the comparative measurements for the spiked filters

Filter No.	**BGN** [a)]	**LGL** [b)]
	Rel. recovery [%]	**Rel. recovery [%]**
Filter 1 and 7	101.8	97.83
Filter 2 and 8	102.2	98.63
Filter 3 and 9	101.9	97.92
Filter 4 and 10	101.3	99.84
Filter 5 and 11	100.2	100.06
Filter 6 and 12	101.6	98.34
Mean value for filters 1 to 6 and filters 7 to 12	**101.5**	**98.8**
Standard deviation *s*	0.7236	0.9614
Rel. standard deviation *s* [%]	**0.71**	**0.97**

[a)] German Social Accident Insurance Institution for the Foodstuffs Industry and the Catering Trade, Mannheim, Germany
[b)] Bavarian State Office for Health and Food Safety, Oberschleißheim Branch, Germany

A mean recovery of 98.8% was obtained when photometric analysis was performed, while the mean recovery using HPLC analysis was 101.5%. The deviation of the results between the two measurement methods was 2.7% and the precision was less than 1.0%.